DOCKET NO.: ISIS-2710

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

KROTZ, et al

Serial No.: 09/032,972 **Group Art Unit: 1623**

Filing Date: February 26, 1998 **Examiner: L. CRANE**

For: METHODS FOR SYNTHESIS OF OLIGONUCLEOTIDES

DATE OF DEPOSIT: 5/8/00

I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL, POSTAGE PREPAID ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231.

Maureen S. Gibbons

TYPED NAME: Maureen S. Gibbons
REGISTRATION NO.: 44, 121

Box ☒ NON-FEE

☐ AF

Assistant Commissioner for Patents
Washington DC 20231

Sir:

AMENDMENT TRANSMITTAL LETTER

Transmitted herewith for filing in the above-identified patent application is:

☐ A Preliminary Amendment.

☒ An Amendment Responsive to the Office Action Dated February 7, 2000.

☐ An Amendment Supplemental to the Paper filed _____.

☐ Other: _____.

☒ Small entity status of this application under 37 C.F.R. 1.9 and 1.27 was established in a previous submission.

☐ A Statement Claiming Small Entity Status under 37 C.F.R. 1.9 and 1.27 is enclosed.

☐ This application is no longer entitled to small entity status. It is requested that this be noted in the files of the Patent and Trademark Office.

☐ Substitute Pages _____ of the Specification are enclosed.

☐ An Abstract is enclosed.

☐ _____ Sheets of Proposed Corrected Drawings are enclosed.

☐ A Certified Copy of each of the following applications: _____ _____ is enclosed.

☐ An Associate Power of Attorney is enclosed.

☐ Information Disclosure Statement.

- ☐ Attached Form 1449.
- ☐ A copy of each reference as listed on the attached Form PTO-1449 is enclosed herewith.

☐ Appended Material as follows: _____ .

☐ Other Material as follows: _____ .

FEE CALCULATION

☒ No Additional Fee is Due.

				SMALL ENTITY		NOT SMALL ENTITY	
	REMAINING AFTER AMENDMENT	HIGHEST PAID FOR	EXTRA	RATE	FEE	RATE	FEE
TOTAL CLAIMS	41	41 (20 MINIMUM)	- 0 -	$9 EACH	$	$18 EACH	$
INDEP. CLAIMS	3	3 (3 MINIMUM)	- 0 -	$39 EACH	$	$78 EACH	$
FIRST PRESENTATION OF MULTIPLE DEPENDENT				$130	$	$260	$
☐ ONE MONTH EXTENSION OF TIME				$55	$	$110	$
☐ TWO MONTH EXTENSION OF TIME				$190	$	$380	$
☐ THREE MONTH EXTENSION OF TIME				$435	$	$870	$
☐ FOUR MONTH EXTENSION OF TIME				$680	$	$1360	$
☐ FIVE MONTH EXTENSION OF TIME				$925	$	$1850	$
☐ LESS ANY EXTENSION FEE ALREADY PAID				minus	($)	minus	($)
☐ TERMINAL DISCLAIMER				$55	$	$110	$
☐ OTHER FEE OR SURCHARGE AS FOLLOWS:							
TOTAL FEE DUE					$ 0		$

☐ A Check is Enclosed in the Foregoing Amount Due.

☐ Petition is hereby made under 37 C.F.R. 1.136(a) to extend the time for response to the Office Action of @@ to and through @@ comprising an extension of the shortened statutory period of @@ month(s).

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

☒ The Commissioner is authorized to charge payment of the following fees and to refund any overpayment associated with this communication or during the pendency of this application to deposit account 23-3050. This sheet is provided in duplicate.

☐ The Foregoing Amount Due for Filing this Paper.

☒ Any additional filing fees required, including fees for the presentation of extra claims under 37 C.F.R. 1.16.

☒ Any additional patent application processing fees under 37 C.F.R. 1.17 or 1.20(d).

SHOULD ANY DEFICIENCIES APPEAR with respect to this application, including deficiencies in payment of fees, missing parts of the application or otherwise, the United States Patent and Trademark Office is respectfully requested to promptly notify the undersigned.

Date: May 8, 2000

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#12
5-25-00

Docket No: ISIS-2710 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Achim H. Krotz et al.

Serial No: 09/032,972 **Group Art Unit: 1623**

Filed: February 26, 1998 **Examiner: L. Crane**

For: Methods for Synthesis of Oligonucleotides

DATE OF DEPOSIT: 5/8/00

I, **Marueen S. Gibbons**, HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL, POSTAGE PREPAID ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231.

Marueen S. Gibbons

TYPED NAME: Maureen S. Gibbons
REGISTRATION NO. 44,121

Assistant Commissioner for Patents
Washington, DC 20231

REQUEST FOR RECONSIDERATION

This is in response to the Office Action dated February 7, 2000.

Claims 1-41 are pending in the present application. Applicants thank the Examiner for indicating that the rejection 35 U.S.C. § 112, has been withdrawn.

All of the pending claims stand rejected under 35 U.S.C.§103(a) as allegedly unpatenable as obvious over U.S. Patent No. 5,705,621 to Ravikumar ("Ravikumar") in view of U.S. Patent No. 4,973,679 to Caruthers et al. ("Caruthers") and further in view of U.S. Patent No. 5,548,076 to Froehler et al. ("Froehler") and further in view of Sproat et al. (PTO-892 Ref.W), Conway, et al. (PTO-892 Ref.Y), Atkinson et al. (PTRO-892 Ref.Z), and Sproat et al. (PTO-892 Ref. RA). Applicants respectfully request withdrawal of the rejection.

The present invention is directed to synthetic procedures for phosphorus-linked oligomers wherein protic acids dissolved in aromatic solvents are used to deprotect of the 5'-hydroxyl group. The use of these solvents provides excellent environmental and economic benefits over methods of the prior art. As the cited references neither teach nor suggest the use of such solvents for the deprotection reaction, Applicants respectfully request that the rejection be withdrawn.

An obviousness determination requires either a suggestion in the prior art to produce the claimed invention or a compelling motivation based on sound scientific principles, accompanied by general knowledge of existence of techniques recognized in the art for carrying out the proposed invention. In re Kranz, 19 USPQ2D 1216 (Bd. Pat. App. & Inter. 1991). Although the Office Action suggests that the references supply the requesite motivation to combine the references, Applicants respectfully disagree. Moreover, assuming that such a motivation exists, which Applicants in no way concede, a combination of the cited references would not result in any process falling within the scope of the present claims.

As stated in the response filed July 6, 1999, it is well known in the art of oligonucleotide synthesis that the efficiencies of the individual nucleotide couplings must be extremely high to provide a useful product. It is therefore apparent that maintenance of very high efficiency (i.e. yield) is critical to successful oligonucleotide syntheses. The Gait reference, also discussed in the Response filed July 6, 1999, indicates the criticality of even small details in established oligonucleotide synthetic protocols, stating on page 18 that:

> It should be recognized that a chemical synthesis method is distinctly different from a biochemical protocol and that a very slight change to a material or method can often make the difference between barely obtaining a usable product and ensuring routinely reliable synthesis.

The Gait reference further states at pages 18-19 that solvent variations can severely impact product yield. Given the Gat reference's disclosure of the sensitivity of oligomer yield to solvent composition, the art skilled would not be motivated to change the solvents customarily used in established protocols for solid phase oligonucleotide synthesis without some indication of success.

None of the cited references indicate that substitution of the solvents employed in the Ravikumar references for the deprotection step with those of the present invention would provide substantial yields of oligonucleotide product. The Office Action suggests that the Ravikumar reference teaches that a "choice of any particular deprotection solvent is ... a choice within the purview of the ordinary practioner" Applicants respectfully disagree. The Ravikumar references specifically teaches the use of methylene chloride and there is no suggestion whatsoever to employ anything but methylene chloride in the deprotection step.

The Office Action states that the Caruthers reference teaches the use of "any solvent which will dissolve the reactants." As best understood by Applicants, the Office Action is suggesting that this statement would motivate one skilled in the art to use any solvent, including those claimed by the present invention. Thus, the Office Action appears to suggest that use of any particular solvent in oligonucleotide synthesis would be obvious, so long as it dissolved the reactants, regardless of how it effected the yield. Although the Office Action states that the Caruthers reference and the Froehler reference motivates the selection of "practically any organic solvent or solvent mixtures which will dissolve the reactants and *not otherwise interfere with the intended synthetic transformation*," it is significant that, neither reference provides any indication whatsoever as to which solvents would not interfere with the "intended synthetic transformation." *See,* Office Action, Page 6 (emphasis added). Further, the synthetic transformation of the present claims relates to the deprotection step. Neither the Caruthers reference, nor the Froehler reference, disclosed the solvents claimed in the present invention for the deprotection step, nor do they suggest which solvents could be successfully employed in the deprotection step, other than the specific solvents disclosed in each. (Specifically, $ZnBr_2$ in nitromethane; methanol and dichloromethane, respectively).

None of the remaining cited references teaches or suggests that the use of the claimed compounds for the deprotection step. Although the Sproat (W), Atkinson, Conway, and the Sproat (RA) references all disclose the use of toluene, they do so only in connection with a **purification**

step. There is no suggestion whatsoever to employ the solvents of the claimed invention in the **deprotection** step, or that such could be used successfully therefor.

As none of the references supply the requisite motivation to combine the references for the purpose of employing the claimed solvents in the deprotection step, there has been no *prima facie* case of obviousness established. The Office Action's assertion that Caruthers and Froehler "grant a considerable degree of latitude to the ordinary practioner in the selection of solvents and reagents for the 5'-O- deprotection step," is not the specific teaching required to support a *prima facie* case of obviousness. Indeed, the cited references disclose many solvents, not all of which would work in the deprotection step. When an obviousness determination depends on a selective combination of prior art references, there must be some reason for the combination other than hindsight gleaned from the invention itself. *Northern Telcom, Inc. v. Datapoint Corp.,* 15 USPQ 1321, 1323, (Fed. Cir. 1990).

Because the cited art does not disclose Applicants' claimed invention, and does not provide motivation to use the same with a reasonable expectation of achieving the high yields of customary protocols, Applicants' claimed invention is not obvious over the cited art. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103 (a).

Applicants believe that the claims are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,

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Date: 5/8/08

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